REMARKS/ARGUMENTS

Claims 15-23 were pending in the application and have been examined. Claims 15-23 currently stand rejected. Applicants respectfully request reconsideration of the pending claims in light of the marks below.

Applicant acknowledges the withdrawal of the various rejections recited in the pending office action. The new rejections are addressed herein below.

New Rejections under 35 U.S.C. § 103(a)

Claims 15-23 are newly rejected under 35 U.S.C. § 103(a) as being unpatentable over US Patent No. 6,849,452, hereafter referred to as Zitvogel *et al.*, in view of WO 01/85920, hereafter referred to as Banchereau *et al.* Zitvogel *et al.* is alleged by the Examiner to teach methods for inducing the activation of NK cells comprising contacting resting NK cells with mature dendritic cells *in vitro* or *ex vivo* (Zitvogel *et al.*, columns 2-3, and columns 29-30, claims 1-11). Further, the Examiner alleges that Zitvogel *et al.* teaches that the dendritic cells can be sensitized to one or more antigens (citing column 12) and that contact between the NK cell and dendritic cell can lead to the proliferation of the NK cell (Zitvogel *et al.*, column 4 and column 16). Still further, the Examiner alleges that Zitvogel *et al.* teaches that the dendritic cells express IL-12, TNF-alpha, IL-15, and IFN α/β and that the NK cells can be part of a population of leukocytes prepared by leukopheresis, or a highly enriched population of resting NK cells comprising more than 70% resting NK cells (columns 13 and 20).

Zitvogel *et al.* is alleged by the Examiner to differ from the instant invention by not teaching that the mature dendritic cells have been produced by contacting dendritic cell precursors with GM-CSF and IL-15. However, Zitvogel *et al.* is alleged by the Examiner to teach that the mature dendritic cells can be produced by culturing bone marrow, which comprises dendritic precursor cells, with GM-CSF and IL-4, followed by maturation induction with LPS. Banchereau *et al.* is alleged by the Examiner to supplement the alleged disclosures of Zitvogel *et al.* by teaching that mature immunostimulatory dendritic cells can be produced by culturing

dendritic cell precursors in the presence of GM-CSF and IL-15, and maturing the dendritic cells by treatment with LPS or CD40L. Banchereau *et al.* further alleged by the Examiner to teach that the mature dendritic cells produced from the culture of dendritic precursors in GM-CSF and IL-15 exhibited expression of CD1a, and high levels of CD80 and CD86. In addition, Banchereau *et al.* is alleged to teach exposing the dendritic cells to an antigen in the form of protein, peptides, or cells expressing the antigen. Still further, the Examiner alleges that Banchereau *et al.* teaches that dendritic cells prepared with IL-15 and GM-CSF are similar in function to dendritic cells prepared with IL-4 and GM-CSF.

The Examiner acknowledges that Banchereau *et al.* did not do a direct comparison of the expression levels of CD1, CD80 and CD86 on dendritic cells produced from cultures in GM-CSF and IL-4, versus GM-CSF and IL-15, the Examiner notes that the IL-15 dendritic cells of Banchereau *et al.* were produced using the same culture conditions, *i.e.* culture in IL-15 and GM-CSF, and appear to express the same markers as the cells recited in the instant methods. "When the structure recited in the reference is substantially identical to that of the claims, claimed properties or functions are presumed to be inherent." Further, Applicant has been reminded by the Examiner that the Office does riot have the facilities for examining and comparing applicant's product with the product of the prior art in order to establish that the product of the prior art does not possess the same material, structural and functional characteristics of the claimed product and that in the absence of evidence to the contrary, the burden is upon the applicant to prove that the claimed products are functionally different than those taught by the prior art and to establish patentable differences.

Based on the teaching alleged above and in view of the alleged similarities in function between mature dendritic cells produced from cultures of dendritic precursor cells exposed to IL-15 and GM-CSF and those produced from cultures of dendritic precursor cells exposed to IL-4 and GM-CSF as taught by Banchereau *et al.*, the Examiner has concluded that it would have been *prima facie* obvious to the skilled artisan at the time of filing to substitute the mature dendritic cells produced from cultures of dendritic precursor cells exposed to IL-15 and

GM-CSF taught by Banchereau for the mature dendritic cells produced from cultures of dendritic precursor cells exposed to IL-4 and GM-CSF in the methods of activating NK cells taught by Zitvogel *et al.* with a reasonable expectation of success that such a substitution would be capable of inducing the activation of NK cells in tissue culture.

Applicant respectfully disagrees with the new rejection of claims 15-23 under 35 U.S.C. § 103(a) as being unpatentable over Zitvogel *et al.*, in view of Banchereau *et al.* Claims 15-23 are directed to methods for inducing the activation and proliferation of natural killer (NK) cells, comprising certain steps recited in the pending claims. Contrary to those claims Zitvogel *et al.* clearly state that their methods are "not accompanied by a large increase in NK cell proliferation, all populations together, but could induce proliferation of a sub-population thereof". (emphasis added). Further, at column 23, lines 53-55 Zitvogel *et al.* state "[n]o significant proliferation was observed under these co-culture conditions as determined by thymidine incorporation after co-culture for 40-70 hours". As such, Zitvogel *et al.* only teach activation of existing NK cells by dendritic cells that have been obtained by the culture of dendritic cell precursors in media containing GM-CSF and IL-4.

Banchereau *et al.* discloses methods for the production of immature dendritic cells from dendritic cell precursors by contact with GM-CSF and IL-15 *in vitro, ex vivo*, or *in vivo*. The immature dendritic cells can further be matured *in vitro* by contact with for example lipopolysaccharide, CD40L, or poly(I):(C). Banchereau *et al.* also note that a certain percentage of the immature dendritic cells have taken on characteristics of Langerhans cells, a subgroup of antigen presenting cells found primarily in the skin. There is no suggestion or disclosure that the dendritic cells produced by the culture in GM-CSF and IL-15 might induce the activation and proliferation of Natural Killer cells as claimed in the instant application. As such, even if assuming one of skill in the art combined the teachings of Zitvogel *et al.* and Banchereau *et al.* the reasonable outcome would be the activation of Natural Killer cells without a significant change in the amount of proliferation. Therefore, the references when consider either separately or in combination do not disclose or suggest the method recited in claims 15-23.

Applicant respectfully requests the Examiner reconsider and withdraw the rejection of claim 15-23 under 35 U.S.C. § 103(a) as being unpatentable over Zitvogel *et al.*, in view of Banchereau *et al.*

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance and an action to that end is respectfully requested. If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 206-467-9600.

Respectfully submitted,

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